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| (21) International Application Number: PCT/IB99/01460 (22) International Filing Date: 12 August 1999 (12.08.99) (30) Priority Data: 9817573.0 12 August 1998 (12.08.98) GB (71) Applicant (for all designated States except US): EDKO TRADING AND REPRESENTATION COMPANY LIMITED [TR/TR]; P.O. Box 228 Sisli, 80233 Istanbul (TR). (72) Inventors; and (75) Inventors/Applicants (for US only): EMBIL, Koral [TR/TR]; Embil Pharmaceutical Company Limited, P.O. Box 226 Sisli, 80223 Istanbul (TR). FIGUEROA, Ray [US/US]; R.F. Technology Consultants, Inc., 8242 N.W. South River Drive, Medley, FL 33166 (US). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS (57) Abstract This invention relates to compositions of nimesulide for topical application. | | |

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NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS

This invention relates to compositions of nimesulide for topical application.

5

Nimesulide is a nonsteroidal anti-inflammatory agent (NSAID), which has poor solubility, especially in water. It has been formulated at various concentrations as a suspension in vehicles containing pharmaceutically acceptable excipients. These vehicles typically consist of aqueous gels containing about 1% nimesulide. Nimesulide in
10 suspension may have limited therapeutic activity, as its percutaneous absorption is impaired by the difficulty of releasing free drug molecules from the suspensoid. Solubilised nimesulide, on the other hand, may offer the advantage of immediate availability of free drug molecules to the receptor site, and gels comprising solubilised nimesulide have been prepared using different pharmaceutical solvents. However, when
15 the gel products comprising solubilised nimesulide are applied topically, they produce an unpleasant yellowish stain on the skin and/or clothing.

Many attempts have been made to provide nimesulide compositions of various kinds. They include those described in EP-A-0782855 and EP-A-0812587. In EP-A-
20 0782855, particles of nimesulide are dispersed (not dissolved) in a base component. In EP-A-0812587, nimesulide is incorporated in a medium vaguely described as a "percutaneous absorption enhancing vehicle base", which comprises water as an essential ingredient and a surfactant such as glyceryl monoolein in an amount of up to 12% w/w.

25 Accordingly, it is an objective of the present invention to provide nimesulide compositions, which are both therapeutically effective and non-staining or substantially non-staining when applied topically. It has been found that this desirable combination of properties is achieved in the compositions of the present invention. The compositions of the present invention may enable the nimesulide to penetrate the upper layer of the skin
30 (stratum corneum) rapidly. Once within the stratum corneum, the nimesulide may be released into the deeper layers of the skin more slowly, which is advantageous in the treatment of the conditions for which nimesulide is used.

The invention provides a composition for topical application comprising nimesulide in a glyceryl monoolein-solvent phase comprising glyceryl monoolein in an amount of 17-59% by weight of the composition.

5 The invention further provides a composition for topical application comprising nimesulide in a glyceryl monoolein-solvent phase, wherein the glyceryl monoolein-solvent phase may have a liquid crystal structure.

The invention further provides a composition for topical application comprising
10 nimesulide, glyceryl monoolein and a non-aqueous solvent. Optionally the composition may also comprise a gelling agent, water and other additives.

The nimesulide is preferably used in the composition in an amount of 0.1-5% by weight, more preferably in an amount of 0.1-3% by weight, most preferably in an amount
15 of around 1% by weight of the composition.

The glyceryl monoolein (or monooleate) may be used in an amount as low as 10-45% by weight, preferably in an amount of 17-45% by weight, more preferably in an amount of 17-59% by weight of the composition. Glyceryl monoolein is available
20 commercially as a distilled monoglyceride mixture with a high monoolein content (for example "GMOorphic" from Eastman Chemicals, USA, or "Glycerol Monooleate" from an alternative manufacturer).

The non-aqueous solvent is preferably used in an amount of 40-82% by weight,
25 more preferably 60-82% by weight of the composition. The solvent should be pharmaceutically acceptable and may for example be a C₁₋₆ alcohol, N-methylpyrrolidone, a glycol or an ether glycol (e.g. a C₂₋₆ compound such as propylene glycol, 1,3-butylene glycol, dipropylene glycol or diethylene glycol), an ether (e.g. a C₂₋₆ ether such as diethyl ether or diethylene glycol monoethyl ether (DGME)), or a C₈₋₂₂ glyceride or ethoxylated
30 glyceride (e.g. capric, caprylic, arachinoic and behanoic glycerides and ethoxylated derivatives thereof, particularly caprylic/capric triglycerides or derivatives containing for example 6 polyoxyethylene units). Mixtures of these solvents can also be used. Preferably a solvent system containing DGME and a C₁₋₆ alcohol such as ethanol is used, preferably

with the DGME in an amount of 35-45% by weight and the alcohol in an amount of 25-35% by weight of the composition. More preferably DGME is used on its own as solvent, preferably in an amount of 40-82% by weight, more preferably in an amount of 60-82% by weight of the composition.

5

The composition may also optionally include a gelling agent such as hydroxypropylcellulose or a fumed silicon dioxide (e.g. Cab-O-Sil). Preferably hydroxypropylcellulose is used. Although gelling agents are not required, they may assist in maintaining the long-term structural integrity and can influence the shelf life stability of a finished product. Gelling agents can additionally offer greater flexibility to the formulator in designing finished products with varied consistence and levels of thickness. Preferably gelling agents are used in an amount of 0.1-10% by weight, more preferably in an amount of 0.5-3% by weight of the composition.

15 The composition need not contain any water. However, it may optionally include water, preferably in amount of up to 15% by weight (for example 5-15% by weight), more preferably in an amount of up to 10% by weight of the composition.

Other ingredients may also optionally be included in the composition, for example 20 capsicum oleoresin, capsaicin, nicotines, camphor, menthol, turpentine oil, preservatives (e.g. propylparaben), antioxidants (e.g. BHT or BHA), sequestrant agents (e.g. EDTA) or colorants (e.g. FD&C Blue 1 or Yellow #5). Preferably such optional additives are included in an amount of up to 0.25% by weight, for example 0.001-0.25% by weight of the composition.

25

Preferably, the composition is in the form of a gel, solution, ointment or spray. Most preferably the composition is in the form of a gel. A gel is easy to apply – it does not drip like a solution may, and the dosage of a gel is usually more easily controlled than that of a spray. The gel may be a jelly-like material, for example formed from a nimesulide 30 solution by the addition of a gelling agent. A nimesulide spray may be a nimesulide solution in a spraying device.

The nimesulide compositions can be used for a variety of indications characterised by pain and inflammation, or stiffness. Such indications are: osteoarthritis of superficial joints, such as the knee, ankle, wrist and elbow; rheumatism; acute musculoskeletal injuries and/or bruising; muscular cramp; strains; sprains; periarthrititis; epicondylitis; 5 tendinitis; bursitis; tenosynovitis; tennis elbow; back strain; lumbago; sciatica; neuralgia; and fibrositis.

The compositions may be prepared by first dissolving the nimesulide in the non-aqueous solvent(s) to form a solution. This solution may be heated to 30-90°C and mixed 10 with glyceryl monoolein, which may have previously been heated to 35-55°C. This mixing step may be followed by agitation and cooling to room temperature to form a clear nimesulide solution.

This clear nimesulide solution may alternatively be prepared by first dissolving 15 glyceryl monoolein in the non-aqueous solvent(s) to form a solution. This solution may be heated to 30-90°C and mixed with nimesulide, followed by agitation and cooling to room temperature to form a clear nimesulide solution.

Optionally, a gelling agent may be mixed into the nimesulide solution, either on its 20 own or as a gel prepared with the non-aqueous solvent(s). If water and other optional additives are included in the composition, these may be mixed into the composition as a final step.

The present invention makes it possible to provide compositions, which have the 25 advantage that they do not leave yellow stains on the skin and clothing upon application. It is believed that the nimesulide compositions of the present invention may be in the form of a liquid crystal structure.

The compositions are applied topically to the skin, which should be clean and is 30 preferably cleansed before use. Cleaning provides a better surface for penetration by the composition, thus assisting in avoiding staining, and prevents surface materials such as salt or grime from complexing with any gelling agent present and coagulating the composition.

The following examples illustrate the invention.

Example 1

| | | |
|---|--|-----------|
| | Diethylene glycol monoethyl ether (DGME) | 42.5% w/w |
| 5 | SD alcohol (ethanol) | 30% w/w |
| | Water | 10% w/w |
| | Nimesulide | 1% w/w |
| | Glyceryl monoolein | 16.5% w/w |

- 10 The nimesulide was dissolved in DGME and ethanol to form a solution, which was heated to 45°C. This heated solution was added to glyceryl monoolein, which had previously been heated to 45°C. The mixture was agitated and cooled to room temperature to give a clear solution, to which water was added.

15 Example 2

| | | |
|----|--|-----------|
| | Diethylene glycol monoethyl ether (DGME) | 40% w/w |
| | SD alcohol (ethanol) | 25.5% w/w |
| | Water | 10% w/w |
| | Fumed silicon dioxide | 7% w/w |
| 20 | Nimesulide | 1% w/w |
| | Glyceryl monoolein | 16.5% w/w |

- 25 The nimesulide was dissolved in DGME and ethanol to form a solution, which was heated to 45°C. This heated solution was added to glyceryl monoolein, which had previously been heated to 45°C. The mixture was agitated and cooled to room temperature to give a clear solution. The gelling agent (silicon dioxide) was then mixed into the solution to the desired consistency to provide a clear gel. Finally water was mixed into the gel.

- 30 Alternatively, the nimesulide was added slowly to DGME at 48-50°C to form a solution. Glyceryl monoolein was heated to 48-50°C and added slowly to the nimesulide solution with mixing to give a clear nimesulide solution, which was cooled to room temperature. Ethanol and gelling agent were mixed thoroughly to form an alcoholic gel,

which was mixed slowly into the nimesulide solution at room temperature to give a clear gel. Finally water was mixed into the gel.

Example 3

| | | |
|----|--|-------------|
| 5 | Diethylene glycol monoethyl ether (DGME) | 42.5% w/w |
| | SD alcohol | 30% w/w |
| | Water | 10% w/w |
| | Nimesulide | 1% w/w |
| | Glyceryl monoolein | 16.475% w/w |
| 10 | Capsaicin | 0.025% w/w |

A clear gel was prepared as described in Example 1. The capsaicin was then added in a final step and mixed into the gel until dissolved and homogenous.

15 Example 4

| | | |
|--|--|---------|
| | Diethylene glycol monoethyl ether (DGME) | 81% w/w |
| | Hydroxypropylcellulose | 1% w/w |
| | Nimesulide | 1% w/w |
| | Glyceryl monoolein | 17% w/w |

20

The nimesulide was dissolved in DGME to form a clear solution, which was heated to 43-47°C. Glyceryl monoolein was heated to 43-47°C and mixed into the solution to form a clear solution, which was mixed and cooled to room temperature. The mixing speed was increased enough to create a vortex of mixing, and hydroxypropylcellulose was

25 added. The mixing was continued until a clear gel was obtained.

Example 5

| | | |
|----|--|-----------|
| | Diethylene glycol monoethyl ether (DGME) | 63.1% w/w |
| | Hydroxypropylcellulose | 1.4% w/w |
| 30 | Nimesulide | 1% w/w |
| | Glyceryl monoolein | 34.5% w/w |

A gel was obtained using the method described in Example 5.

Example 6

| | |
|--|---------|
| Diethylene glycol monoethyl ether (DGME) | 82% w/w |
| Nimesulide | 1% w/w |
| 5 Glyceryl monoolein | 17% w/w |

The nimesulide was dissolved in DGME to form a clear solution, which was heated to 43-47°C. Glyceryl monoolein was heated to 43-47°C and mixed into the solution to form a clear solution, which was mixed and cooled to room temperature.

10

Upon visual inspection, a clear transparent medium was observed and no nimesulide crystals were observed, suggesting that the nimesulide was only present in solution. The compositions of the Examples were also found to be physically stable, for example it was possible to keep them at 40°C for 60 days or more.

15

Claims

1. A composition comprising nimesulide in a glyceryl monoolein-solvent phase
5 comprising glyceryl monoolein in an amount of 17-59% by weight of the composition.
2. A composition comprising nimesulide in a glyceryl monoolein-solvent phase,
wherein the glyceryl monoolein-solvent phase has a liquid crystal structure.
- 10 3. A composition comprising nimesulide in an amount of 0.1-5% by weight of the
composition, glyceryl monooleate in an amount of 17-59% by weight of the composition
and a non-aqueous solvent in an amount of 40-82% by weight of the composition.
4. A composition according to claim 3, wherein the nimesulide is used in an amount
15 of 0.1-3% by weight, preferably in an amount of about 1% by weight of the composition.
5. A composition according to claim 3 or 4, wherein the non-aqueous solvent is a
solvent system containing DGME in an amount of 35-45% by weight and ethanol in an
amount of 25-35% by weight of the composition.
20
6. A composition according to any of claims 3 or 4, wherein the non-aqueous solvent
is DGME used in an amount of 40-82% by weight, preferably in an amount of 60-82% by
weight of the composition.
- 25 7. A composition according to any of claims 3 to 6, which further comprises a gelling
agent in an amount of 0.5-3% by weight of the composition.
8. A composition according to claim 7, wherein the gelling agent is
hydroxypropylcellulose.
30
9. A composition according to any of claims 3 to 8, which further comprises water in
an amount of 0-15% by weight of the composition.

10. A composition according to claim 9, wherein water is used in an amount of 0-10% by weight of the composition.
11. A composition according to claim 9 or 10, wherein the composition does not
5 contain any water.
12. A composition according to any of claims 3 to 11, which further comprises at least one other additive in an amount of up to 0.25% by weight, preferably 0.001-0.25% by weight of the composition.
- 10 13. A composition according to claim 12, wherein the at least one other additive is selected from the group consisting of capsicum oleoresin, capsaicin, nicotines, camphor, menthol, turpentine oil, preservatives such as propylparaben, antioxidants such as BHT or BHA, sequestrant agents such as EDTA or colorants such as FD&C Blue 1 or Yellow #5.
- 15 14. A composition according to any preceding claims, wherein the composition is in the form of a gel, solution, ointment or spray; preferably a gel.
15. A process for the preparation of a composition according to any preceding claims,
20 which comprises the following steps:
(i) dissolving nimesulide in non-aqueous solvent(s) to form a solution, which is heated to 30-90°C;
(ii) mixing this solution with glyceryl monoolein, which has previously been heated to 35-55°C;
25 (iii) followed by agitation and cooling to room temperature to form a clear nimesulide solution.
16. A process for the preparation of a composition according to any preceding claims, which comprises the following steps:
30 (i) dissolving glyceryl monoolein in non-aqueous solvent(s) to form a solution, which is heated to 30-90°C;
(ii) mixing this solution with nimesulide;

(iii) followed by agitation and cooling to room temperature to form a clear nimesulide solution.

17. The process of claim 15 or 16, further comprising the step of:

5 (iv) mixing a gelling agent into the nimesulide solution, either on its own or as a gel prepared with the non-aqueous solvent(s).

18. The process of any of claims 15 to 17, further comprising the step of:

(v) mixing water into the solution or gel.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/18 A61K9/127 A61K47/14 A61K47/10

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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